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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/550,647	09/27/2005	Tanjore SoundaRajan Balganesh	101009-1P US	4534

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ASTRAZENECA R&D BOSTON
35 GATEHOUSE DRIVE
WALTHAM, MA 02451-1215

EXAMINER	
MONDESI, ROBERT B	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/550,647	BALGANESH ET AL.	
	Examiner	Art Unit	
	Robert B. Mondesi	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 September 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *February 2, 2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' election of Invention of Group I, Claims 1-7, in response to the restriction requirement mailed August 2, 2007 is acknowledged. Because applicants did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Therefore the requirement is still deemed proper and is made FINAL.

Status of the claims

Claims 8-12 have been canceled. **Claims 1-7** are pending and are presently under examination.

Priority

The current application filed on September 27, 2005 is a 371 of PCT/GB04/01272 03/23/2004, which in turn claims priority to foreign application, UNITED KINGDOM 03073293 filed on 03/29/2003. A certified copy of foreign document UNITED KINGDOM 03073293 has been provided.

Drawings

Drawings filed September 27, 2005 have been accepted.

Information Disclosure Statement

The IDS filed February 2, 2006 has been received and is signed and considered, a copy of the PTO 1449 is attached to the following document.

Specification

The disclosure is objected to because of the following informalities:

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: a method for attenuating a microorganism.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting the growth of *Myobacterium tuberculosis* comprising the inhibition of IDH kinase, *pknG* which leads to the inhibition of isocitrate dehrogenase ,*icd1*, does not reasonably provide enablement for a method for attenuating a microorganism which comprises inhibiting in the microorganism a metabolic pathway essential for viability, by promoting use of the substrate of the pathway in a different metabolic pathway which is non-essential to the microorganism whereby the substrate is unavailable to the essential pathway and the micro organism is attenuated. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is

required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir.1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.'" (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the predictability or unpredictability of the art, (5) the relative skill of those in the art, (6) the amount or direction or guidance presented, (7) the presence or absence of working examples, and (8) the quantity of experimentation necessary. Although the quantity of experimentation alone is not dispositive in a determination of whether the required experimentation is undue, this factor does play a central role. For example, a very limited quantity of experimentation may be undue in a fledgling art that is unpredictable where no guidance or working examples are provided in the specification and prior art, whereas the same amount of experimentation may not be undue when viewed in light of some guidance or a working example or the experimentation required is in a predictable established art. Conversely, a large quantity of experimentation would require a correspondingly greater quantum of guidance, predictability and skill in the art to

overcome classification as undue experimentation. In Wands, the determination that undue experimentation was not required to make the claimed invention was based primarily on the nature of the art, and the probability that the required experimentation would result in successfully obtaining the claimed invention. (Wands, 8 USPQ2d 1406). Thus, a combination of factors which, when viewed together, would provide an artisan of ordinary skill in the art with an expectation of successfully obtaining the claimed invention with additional experimentation would preclude the classification of that experimentation as undue. A combination of Wands factors, which provide a very low likelihood of successfully obtaining the claimed invention with additional experimentation, however, would render the additional experimentation undue.

1-2 .Breadth of the claims and the nature of the invention..

In regards to the method of the invention and the breadth of the claims the broadest interpretation that applies is a method for attenuating a microorganism which comprises inhibiting in the microorganism a metabolic pathway essential for viability, by promoting use of the substrate of the pathway in a different metabolic pathway which is non-essential to the microorganism whereby the substrate is unavailable to the essential pathway and the micro organism is attenuated.

3-4. The state of prior art and the level of predictability in the art.

The level of predictability is low in the art with regards to the claimed method of the invention.

Ikeda et al., 1991 teach that the accumulation of toxic metabolites and the depletions of cellular energy and NADPH resulting from the excessive inhibition of IDH are each likely to have been detrimental to
cell growth. However, the relative contributions of each mechanism remain to be determined. To address this question, we will need to measure the fluxes of both the glyoxylate bypass and the Krebs cycle and the cellular levels of key metabolites.

Ikeda et al. teach further that to date, the only substrate which has been identified for IDH kinase/phosphatase is IDH. The possibility that IDH is the sole substrate for this bifunctional regulatory protein is supported by genetic as well as biochemical evidence. Strains with null alleles of aceK can be restored to growth on acetate by second-site mutations in icd, the gene encoding IDH. These mutations reduce the level of IDH activity and so eliminate the need for the phosphorylation and consequent inhibition of this enzyme. The phenotype produced by the selective loss of IDH phosphatase is also consistent with the suggestion that IDH is the only key substrate for IDH kinase/phosphatase; cells expressing aceK3 are phenotypically identical to cells carrying null mutations in icd.

5. The relative skill in the art.

The relative skill in the art as it relates to the method of the invention is characterized by that of a M.D. or Ph. D. level individual.

6-7. The amount of guidance present and the existence of working examples.

The applicant has provided some guidance in regards to a method of inhibiting the growth of *Myobacterium tuberculosis* comprising the inhibition of IDH kinase, *pknG* which leads to the inhibition of isocitrate dehrogenase ,*icd1*, by providing Examples 1-2 and table 1, see specification of the instant application on pages 1-13.

Applicants have not provided any guidance with the regards to the broad scope of a method for attenuating a microorganism which comprises inhibiting in the microorganism a metabolic pathway essential for viability, by promoting use of the substrate of the pathway in a different metabolic pathway which is non-essential to the microorganism whereby the substrate is unavailable to the essential pathway and the micro organism is attenuated.

8. The quantity of experimentation necessary.

The amount of experimentation that is required is undue: while a method of inhibiting the growth of *Myobacterium tuberculosis* comprising the inhibition of IDH kinase, *pknG* which leads to the inhibition of isocitrate dehrogenase ,*icd1* might be considered routine, a method for attenuating a microorganism which comprises inhibiting in the microorganism a metabolic pathway essential for viability, by promoting use of the substrate of the pathway in a different metabolic pathway which is non-essential to the microorganism whereby the substrate is unavailable to the essential pathway and the micro organism is attenuated is not routine and requires more experimentation. Therefore, in view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, and the high degree of unpredictability as evidenced by the prior art, undue experimentation would be

necessary for a skilled artisan to make and use the entire scope of the claimed invention.

It must be noted that the issue in this case is the breath of the claims in light of the predictability of the art as determined by the number of working examples, the skill level of the artisan and the guidance presented in the instant specification and the prior art of record. The Applicants make and test position is inconsistent with the decisions of *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) where it is stated that "... scope of claims must bear a reasonable correlation to scope of enablement provided by the specification to persons of ordinary skill in the art...". Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See *In re Wands*, 858 F.2d at 737, 8 USPQZd at 1404 (Fed. Cir. 1988). Therefore, for the instant specification to be enabling, it needs to provide direction/guidance regarding an acceptable number of different enzymes in different microorganisms.

Absent sufficient guidance/direction one of skill in the art would not be able to practice the claimed invention commensurate in scope with the claims. Thus, for all these reasons, the specification is not considered to be enabling for one skilled in the art to make and use the claimed invention as the amount of experimentation required is undue, due to the broad scope of the claims, the lack of guidance and insufficient working examples provided in the specification and the high degree of unpredictability as evidenced by the state of the prior art, attempting to test all the different type

enzymes in different microorganisms encompassed by the claimed invention would constitute undue experimentation. Therefore, applicants have not provided sufficient guidance to enable one of skill in the art to make and use the claimed invention in a manner that reasonably correlates with the scope of the claims, to be considered enabling.

Claims 4-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 is a depended claim that depends form itself and therefore it is not clear as to what the intended limitations of the claim encompasses.

Claim 5 is a dependent claim that does not remedy the deficiencies of the independent claim that it depends from.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Hariharan et al., 1999.

In regards to **claims 1-2** applicants are informed that the claims do not contain an active step, "inhibiting a pathway by promoting the substrate of the pathway in a different metabolic pathway" is not in actuality a step. The act promoting requires a step, the applicants must disclose "an event" that contributes to the promoting and therefore the attenuating of a microorganism. The only active steps of the invention are disclosed in **claims 3, 5 and 7**; wherein it is indicated that an enzyme such as a kinase, icd1, or pknG is inhibited. Furthermore it needs to be pointed out that the act inhibition of icd1 or pknG is done indirectly, wherein it is the kinase that phosphorylizes the said enzymes is inhibited and as an affect icd1 or pknG are inhibited.

Hariharan et al. teach a method of identifying potent enzyme inhibitors through a robust HTS assay. Hariharan et al. teach further that they have developed a HTS assay that mimics a crucial step in an essential metabolic pathway, the purine salvage pathway of the malarial parasite Plasmodium falciparum. In this assay we have used purified recombinant enzymes: hypoxanthine guanine phosphoribosyl transferase (HGPRT) and inosine monophosphate dehydrogenase (IMPDH) from the malarial parasite and the human host, respectively. These two enzymes, which work in tandem, are used to set up a coupled assay that is robust enough to meet the stringent criteria of an HTS assay. In the first phase of our screen we seem to have identified novel inhibitors that kill the parasite by inhibiting the salvage pathway of the parasite (Abstract, Page 187).

Thus Hariharan et al. et al. teach all the elements of **claims 1-4** and these claims are anticipated under 35 USC 102(b).

Claims 1-5 are rejected under 35 U.S.C. 102(b) as being anticipated by Ikeda et al., 1991.

In regards to **claims 1-2** applicants are informed that the claims do not contain an active step, "inhibiting a pathway by promoting the substrate of the pathway in a different metabolic pathway" is not in actuality a step. The act promoting requires a step, the applicants must disclose "an event" that contributes to the promoting and therefore the attenuating of a microorganism. The only active steps of the invention are disclosed in **claims 3, 5 and 7**; wherein it is indicated that an enzyme such as a kinase, icd1, or pknG is inhibited. Furthermore it needs to be pointed out that the act inhibition of icd1 or pknG is done indirectly, wherein it is the kinase that phosphorylizes the said enzymes is inhibited and as an affect icd1 or pknG are inhibited.

Ikeda et al. teach a method for attenuating a microorganism which comprises inhibiting in the microorganism a metabolic pathway essential for viability, by promoting use of the substrate of the pathway in a different metabolic pathway which is non-essential to the microorganism whereby the substrate is unavailable to the essential pathway and the micro organism is attenuated, wherein the microorganism is Mycobacterium tuberculosis and wherein the enzyme to be inhibited is isocitrate dehydrogenase page 73, column 1, paragraph 2, lines 20-29 through column 2, paragraph 4, lines 1-14).

Thus Ikeda et al. et al. et al. teach all the elements of **claims 1-5** and these claims are anticipated under 35 USC 102(b).

Claims 1-4 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Sacchettini et al. United States Patent Application Pub No. US 2003/0018166.

In regards to **claims 1-2** applicants are informed that the claims do not contain an active step, "inhibiting a pathway by promoting the substrate of the pathway in a different metabolic pathway" is not in actuality a step. The act promoting requires a step, the applicants must disclose "an event" that contributes to the promoting and therefore the attenuating of a microorganism. The only active steps of the invention are disclosed in **claims 3, 5 and 7**; wherein it is indicated that an enzyme such as a kinase, icd1, or pknG is inhibited. Furthermore it needs to be pointed out that the act inhibition of icd1 or pknG is done indirectly, wherein it is the kinase that phosphorylizes the said enzymes is inhibited and as an affect icd1 or pknG are inhibited.

Sacchettini et al. teach that the invention provides methods and compositions for use in identifying inhibitors of biochemical pathways important for persistent infection, allowing the identification and/or design of improved therapeutics for treating persistent infections by pathogenic microbes. Particularly disclosed is the importance of the glyoxylate shunt to the persistent phase of various infectious agents, including Mycobacteria, such as M. tuberculosis, and the identification of preferred targets for drug development, including the enzymes isocitrate lyase (ICL) and malate synthase. Crystals and three-dimensional structures of M. tuberculosis ICL, without ligand and in

complex with two inhibitors are also disclosed, for exemplary use in the design of inhibitors and therapeutic agents (abstract).

Sacchettini et al. teach further that socitrate lyase competes with the TCA cycle enzyme isocitrate dehydrogenase for their common substrate isocitrate. By changing the total cellular activity of either of the two enzymes and/or by changing their affinities toward isocitrate, control of carbon flux between the two cycles is achieved. In E. coli, growth on acetate leads to a decrease in NADP.sup.+-dependent isocitrate dehydrogenase activity caused by the reversible phosphorylation of isocitrate dehydrogenase. The corresponding isocitrate dehydrogenase-kinase is encoded in the same operon as the isocitrate lyase and the malate synthase. The reduction in isocitrate dehydrogenase activity redirects isocitrate into the glyoxylate cycle through the activity of isocitrate lyase. The phosphorylation-dephosphory- lation of isocitrate dehydrogenase is believed to regulate entry of the substrate into the glyoxylate shunt. In addition, E. coli isocitrate lyase is inhibited by several metabolites, e.g., succinate, 3-phosphoglycerate or phosphoenolpyruvate, leading to a more subtle control of the carbon flux (page 15; paragraph 0201).

Sacchettini et al. also teach that The inhibition of Icl activity by several compounds, known to be effective against various isocitrate lyases, was examined. Itaconate, itaconic anhydride, bromopyruvate, and 3-nitropropionate were found to be the most potent inhibitors, with inhibition constants of 120, 190, 120, and 3 .mu.M, respectively. Interestingly, at saturating substrate conditions succinate did not reveal any inhibitory effect on the recombinant enzyme. Oxalate and malate were also shown

to inhibit the activity to approximately 50% at 5 mM inhibitor concentration. 3-Phosphoglycerate, 6-phosphogluconate, fructose-1,6-bisphosphate, and malonic acid had no inhibitory effect. Most of the effectors can be classified as structural analogs of the reaction products succinate (itaconate, itaconic anhydride, and 3-nitropropionate) or glyoxylate (3-bromopyruvate and oxalate) (page 16; paragraph 0211).

Sacchettini et al. teach that the requirement of ICL to a persistent infection makes it an attractive target for drug discovery. Prior to the present invention, screening for inhibitors against ICL was extremely complex and used infected macrophages or mice. The approach of the present inventors is to screen compounds, first for inhibitory activity against the enzyme and then for mycobacterial survival The inventors have now developed a rapid drug screening strategy using a mutant complemented with the M. tuberculosis *icl* gene (page 20 paragraph 0248 through lines 1-2 of paragraph 0249).

Thus Sacchettini et al. et al. teach all the elements of **claims 1-4 and 6** and these claims are anticipated under 35 USC 102(b).

Claims 1-4 and 6-7 are rejected under 35 U.S.C. 102(e) as being anticipated by WO 03/074728 (cited in the IDS filed February 2, 2006).

In regards to **claims 1-2** applicants are informed that the claims do not contain an active step, "inhibiting a pathway by promoting the substrate of the pathway in a different metabolic pathway" is not in actuality a step. The act promoting requires a step, the applicants must disclose "an event" that contributes to the promoting and therefore the attenuating of a microorganism. The only active steps of the invention are disclosed in **claims 3, 5 and 7**; wherein it is indicated that an enzyme such as a kinase, icd1, or

pknG is inhibited. Furthermore it needs to be pointed out that the act inhibition of icd1 or pknG is done indirectly, wherein it is the kinase that phosphorylizes the said enzymes is inhibited and as an affect icd1 or pknG are inhibited.

WO 03/074728 teaches a method for attenuating a microorganism which comprises inhibiting in the microorganism a metabolic pathway essential for viability, by promoting use of the substrate of the pathway in a different metabolic pathway which is non-essential to the microorganism whereby the substrate is unavailable to the essential pathway and the micro organism is attenuated, wherein the microorganism is Mycobacterium tuberculosis and wherein the enzyme to be inhibited is pknG (page 36, lines 12-33 through page 40, lines 1-23).

Thus Sacchettini et al. et al. teach all the elements of **claims 1-4 and 6-7** and these claims are anticipated under 35 USC 102(e).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert B. Mondesi whose telephone number is 571-272-0956. The examiner can normally be reached on 9am-5pm, Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Robert B Mondesi
Examiner
Art Unit 1652

RBM

10-16-07